REMARKS

Reconsideration and withdrawal of the rejections of this application are respectfully requested.

I. Status of Claims and Formal Matters

Claims 1, 7-9, 14,15 and 19-29 are under examination in this application.

II. The Rejections Under 35 U.S.C. § 112 Are Overcome

Claims 1, 7-9, 14, 15 and 19-29 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully disagree and traverse this rejection.

In the Response to the Office Action dated April 11, 2005, the limitation "not to central receptors" was added to the pending claims. The limitation was intended to more precisely specify that the active agents of the invention (i.e., morphine and ketamine) function through local receptors in the periphery and not through central receptors of the central nervous system. In response to this amendment, it is now alleged that "the claims contain subject matter that is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

A comprehensive reading of the specification easily conveys to one skilled in the art that the exclusion of systemic effects mediated by central receptors was a well described embodiment of the invention. For example, page 15, lines 13-19 discourages the administration of ketamine to central receptors. This passage states:

> Except for dextromethorphan, many current NMDA receptor agonists have not been suitable for systemic clinical use due to profound psychomimetic effects. Such NMDA receptor antagonists, however, may be used in the present invention in topical formulations.

Here, the specification makes clear that ketamine would not be provided to central receptors. Examples 2-7 describe topical administration of an opioid, such as morphine or M6G, to the tails of mice. Examples 6-7 describe topical administration of an NMDA receptor antagonist, such as

MK801 or ketamine, to the tails of mice. The effect of this topical administration paradigm was localized to the peripheral receptors and excluded central receptors, as stated on page 20, lines 1-10 and lines 23-25:

> The tail immersion technique has a number of advantages. Foremost is the ability to repeatedly treat the mice without tissue damage secondary to injections. The paradigm was selective for local mechanisms. Testing proximal regions of the tail failed to reveal any analgesic response, confirming the distribution studies with ^{125}I-opioid which documented the localization of the radiolabel only to the regions immersed in drug solution and the absence of any detectable uptake into the blood or the central nervous system. ... In all cases, proximal segments of the tail which were not exposed to the opioid solution were not analgesic, confirming the peripheral site of action for the sites immersed in the opioid solution.

Thus, delivery of the active agents "to local peripheral receptors and not to central receptors" is not only extensively described, but specifically exemplified in the instant specification.

Accordingly, one skilled in the art reading the passage on page 9, lines 28-35 (where it is stated that the topical formulations of the invention are not required to deliver the active ingredients to the central receptors), would instantly recognize that the alternative embodiments of the invention where central delivery was not required were intended to exclude delivery from the central receptors altogether.

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112 are requested.

III. The Rejections Under 35 U.S.C. § 103 Are Overcome

Claims 1, 9, 14, 15, 19-23, 26 and 27 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yakesh (U.S. Patent No. 5,849,761; hereinafter "Yakesh") in view of Mayer *et al.* (U.S. Patent No. 5,635,204; hereinafter "Mayer"). It is alleged that the combination of Yakesh and Mayer renders obvious a topical composition comprising morphine, ketamine and an excipient. Applicants respectfully disagree and traverse the rejection. It is respectfully asserted that the cited references fail to teach or suggest a composition comprising morphine, ketamine and an excipient for exclusive use in the periphery.

Yakesh describes and claims methods of using anti-diarrheal compounds that interact with peripheral opiate receptors but that do not elicit central nervous system side effects. To demonstrate the need for these anti-diarrheal compounds, Yakesh elaborates on the problems in the art. At column 3, lines 66-67, through column 4 lines 1-8 Yakesh states:

> Opiates, such as morphine, however, when peripherally applied, have a short duration of action and possibly can, if applied at sufficient levels, have effects upon consciousness and respiration. The possible systemic effects, CNS effects and abuse potential render conventional opioids **unsuitable for local application** and unsuitable as peripheral anti-hyperalgesics. Thus, there is a need for effective anti-hyperalgesics that directly block peripheral sensitization, but that do not have concomitant central nervous system effects, including the potential for abuse (emphasis added).

Yakesh does not teach a topical composition comprising morphine, ketamine or morphine and ketamine for exclusive use in the periphery. Instead, Yakesh teaches away from the use of "conventional opioids" in the periphery by alerting one skilled in the art to the problems associated with their use and providing an alternate therapeutic regimen.

Mayer teaches a drug combination comprising a first analgesic, a second component and an NMDA receptor antagonist. Mayer teaches only systemic administration of the drug combination. Mayer is silent regarding the significant role that peripheral sites play in the development of tolerance, and the dose-lowering effect of NMDA receptor antagonists on opioids in the periphery. Accordingly, Mayer does not teach a topical composition or method for exclusive use in the periphery, much less suggest any need therefor.

For the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988). There must also be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993).

At the time the application for the present invention was filed, there was no reasonable expectation of success in practicing the claimed invention. As previously documented in the Office Action Response dated April 11, 2005, several medical reports published both before and

after the filing of the present application teach that in clinical applications, morphine fails to stimulate peripheral sites. *See,* for example, Moore (1994), Picard (1997) and Yarussi (1999), previously cited. These studies demonstrate that the effectiveness of tolerance attenuated doses of morphine in the periphery was unexpected given the state of the art. Nothing in Yakesh challenges or contradicts this understanding of the state of the art with respect to topical morphine.

In the present Office Action, it is alleged that the claimed invention is obvious because "Yakesh teaches that it is known in the art that the concentration of morphine must be sufficiently low to avoid systemic and CMS side effects." However, given the lack of efficacy reported for topical morphine, acknowledged even by Yakesh (reporting its short duration of action), low doses of morphine for exclusive use in the periphery would not have been the obvious choice for the skilled practitioner. The teachings of Mayer provide no more encouragement to the skilled practitioner, as Mayer fails to teach or suggest a dose lowering effect of ketamine on morphine analgesia in the periphery.

The requisite expectation of success must be found in the prior art, and not the Applicants' disclosure. *Id.* The cited references provide no reasonable expectation of success in practicing the claimed invention. It is only the teaching in the Applicants' disclosure that shows the dose lowering effect of ketamine on morphine analgesia exclusively in the periphery, thereby enabling effective compositions and methods comprising topical morphine.

Furthermore, there is no motivation for the skilled artisan to look to the teachings of Yakesh, much less modify the teachings of the same in view of Mayer to localize and manage morphine analgesia in the periphery. The present Office Action states that "Yakesh teaches that the formulation of morphine for only peripheral use is known in the art when concentrations are sufficiently low." To the contrary, what Yakesh teaches is that the use of morphine in the periphery is "**unsuitable for local application**" due to its short duration of action and high potential for side effects. Yakesh does not teach, suggest or provide any reasonable expectation of success for topical morphine compositions in the periphery. Rather, Yakesh rejects the use of morphine in the periphery and provides clear alternatives to this course of treatment.

As stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the

modification." Yakesh clearly discourages the use of conventional opioids, such as morphine, in the periphery. Mayer is silent regarding the significant role that peripheral sites play in the development of tolerance, and the dose-lowering effect of ketamine on morphine in the periphery. Thus, in the present Office Action, the art is only modified as suggested by the Examiner, as Yakesh and Mayer fail to provide any indication of the desirability for making such modifications to provide morphine analgesia selectively to the periphery.

Claims 7, 8, 24, 25, 28 and 29 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yakesh and Mayer *et al.* and further in view of Mackles *et al.* (U.S. Patent No. 5,322,683; hereinafter "Mackles"). Applicants respectfully disagree and traverse the rejection.

Dependent claims 7, 8, 24, 25, 28 and 29 further comprise a local anesthetic (e.g., lidocaine), or the use thereof, in the claimed compositions and methods of the invention. The Office Action indicates that rejections in view of Yakesh and Mayer are applied to claims 7, 8, 24, 25, 28 and 29 as they are to claims 1, 7-9, 14, 15 and 19-29. Mackles is therefore further cited in combination with Yakesh and Mayer for its disclosure of the topical use of lidocaine.

As described herein above, Yakesh and Mayer fail to teach or suggest a composition comprising morphine, ketamine and an excipient for exclusive use in the periphery. There is no additional disclosure in Mackles that cures the defects of Yakesh and Mayer. Accordingly, Yakesh, Mayer and Mackles fail to teach or suggest the claimed invention.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §103 are requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested; and, the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the amendments and remarks herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 04-1105.

Respectfully submitted,

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